

## REMARKS

Applicants have amended claims 5-15 to correct the objection based on multiple dependent claims depending on another multiple dependent claim. Further, Applicants have amended claim 1 to better define the subject matter that Applicants regard as the invention. The present invention relates to a process for making 3-isochromanone by the catalyzed carbonylation of o-xylene- $\alpha,\alpha'$ -dihalide using carbon monoxide. The novelty of the process lies in the use of a hindered amine base as a hydrogen halide capturing agent and carrying out the carbonylation in a tertiary alcohol/water medium where the ratio of water to tertiary amine is in the range of 1:1 to 20:1.

Claims 1-15 stand rejected under 35 U.S.C. §102(b) as being anticipated by Hirai et al. (US 5,886,211). Hirai et al. describes a process for producing 3-isochromanones by reacting an  $\alpha,\alpha'$ -o-xylene dihalide derivative with carbon monoxide and water in an organic solvent in the presence of a hydrogen halide capturing agent and a catalyst to obtain a reactant, and then treating the reactant with an acid.

Hirai et al.'s process differs from Applicants invention in two main respects:

1. Hirai et al.'s process uses a different base. In sixteen of the examples (Examples 4, 5, 7, 11-23) calcium hydroxide is used as the base. In the other four (Examples 6, 8-10), sodium hydroxide is used as the base. Although the patent states that tertiary amines may be used, there are no examples of the process using a hindered amine base as claimed by Applicants. Applicants have discovered that by using a hindered amine base in combination with a specific ratio of water to alcohol medium, the reaction produces acceptable yields and has improved industrial applicability.
2. Hirai et al. points one skilled in the art in the direction of using less water than solvent. In all examples except five (Examples 6, 8-10 and 15) less than one mole of water is used for each mole of solvent. The four main exceptions are the examples that employ sodium hydroxide as the base (Examples 6, 8-10). The yield of 3-isochromanone obtained in Examples 6 and 8-10 is much lower and would discourage a skilled person from using these conditions<sup>2</sup>. The other exception is Example 15. In this example the water to solvent molar ratio is 1.07:1. However, the water is added gradually during the process and immediately before the final

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<sup>2</sup> The yields obtained using calcium hydroxide as base range from 51.3% (Examples 12 and 20) to 87.4% (Example 5) and average out at 69.3% (72.8% if Examples 19, 20 and 21, which appear to be exactly the same as Examples 11, 12 and 14, are discounted). Whereas the yields obtained using sodium hydroxide as base range from 6.7% (Example 10) to about 55% (Example 6) and average out at 35.3%. The superior yield obtained using calcium hydroxide as base is clearly the basis for the comment that alkaline earth metal bases are "still preferred for better yield" (col. 7, lines 51-52).

addition the molar ratio of water to solvent is 0.91:1.0. Thus, for the most part, the reaction is carried out using less water than solvent. Applicants' process, as amended, requires the molar ratio of water to tertiary alcohol to be in the range 1:1 to 20:1.

For convenience, a summary of the molar ratios of the reactants used and yields obtained in both the Applicants' Examples and Hirai's Examples is shown below.

Present Invention:

| Example | Mole ratios |       |         |       | Yield            | Comments         |
|---------|-------------|-------|---------|-------|------------------|------------------|
|         | OXDC        | Base  | Alcohol | water |                  |                  |
| 1       | 1.000       | 3.000 | 4.000   | 10    | 70.6             | Catalyst recycle |
| 2       | 1.000       | 3.000 | 4.800   | 10    | 75.4             |                  |
| 3       | 1.000       | 3.125 | 3.750   | 10    | 83.7             |                  |
| 4       | 1.000       | 2.500 | 2.038   | 20    | 75.8             |                  |
| 5       | 1.000       | 2.800 | 3.000   | 17.5  | 82.5             |                  |
| 6       | 1.000       | 3.000 | 4.800   | 10    | 75.8             |                  |
| 7       | 1.000       | 3.000 | 3.750   | 20    | 82.3, 69.9, 73.7 |                  |
| 8       | 1.000       | 3.000 | 3.000   | 20    | 81               |                  |
| 9       | 1.000       | 3.000 | 3.080   | 20    | 84.5             |                  |

Hirai et al. (EP-A-0834497)

| Example | Mole ratios |       |         |       | Yield | Comments                  |
|---------|-------------|-------|---------|-------|-------|---------------------------|
|         | OXDC        | Base  | Alcohol | Water |       |                           |
| 4       | 1.000       | 2.100 | 26.98   | 8.88  | 76.7  | Sodium hydroxide base     |
| 5       | 1.000       | 2.100 | 26.98   | 10.00 | 87.4  |                           |
| 6       | 1.000       | 3.200 | 5.40    | 28.00 | ~55   |                           |
| 7       | 1.000       | 3.260 | 26.98   | 3.11  | 74.3  | Sodium hydroxide base     |
| 8       | 1.000       | 3.200 | 5.40    | 3.11  | 39.2  |                           |
| 9       | 1.000       | 3.200 | 5.40    | 28.00 | 40.2  |                           |
| 10      | 1.000       | 3.200 | 5.40    | 28.00 | 6.7   | Sodium hydroxide base     |
| 11      | 1.000       | 2.100 | 26.98   | 3.33  | 54.6  | Gradual addition of water |
| 12      | 1.000       | 2.100 | 26.98   | 8.88  | 51.3  |                           |
| 13      | 1.000       | 2.100 | 26.98   | 14.44 | 81.2  |                           |
| 14      | 1.000       | 2.100 | 26.98   | 22.20 | 57.6  |                           |
| 15      | 1.000       | 2.100 | 13.52   | 14.44 | 81.6  |                           |
| 16      | 1.000       | 2.100 | 26.98   | 20.00 | 82.5  |                           |
| 17      | 1.000       | 2.100 | 20.32   | 14.00 | 84.7  |                           |
| 18      | 1.000       | 2.100 | 20.34   | 19.80 | 83.0  |                           |
| 19      | 1.000       | 2.100 | 26.98   | 3.33  | 54.6  |                           |
| 20      | 1.000       | 2.100 | 26.98   | 8.88  | 51.3  |                           |
| 21      | 1.000       | 2.100 | 26.98   | 22.22 | 57.6  |                           |
| 22      | 1.000       | 2.100 | 26.98   | 3.33  | 58.1  |                           |
| 23      | 1.000       | 2.100 | 40.47   | 16.66 | 72.9  |                           |

The problem with Hirai et al.'s process is that, despite what is said under "Industrial Applicability" in the passage bridging columns 18 and 19, it does not lend itself to scaling up to a practical and efficient manufacturing process. The main reasons are as follows.

1. In the section on "Industrial Applicability" Hirai et al. clearly prefers to use an inorganic base as the hydrogen halide-capturing agent (column 18, line 63). The preferred inorganic base is calcium hydroxide, which has the disadvantage of being a solid. The bulk handling of solids on an industrial scale is a more demanding operation than the bulk handling of liquids. Further, inorganic bases are consumed in the chemical process and cannot be re-cycled in the carbonylation stage. Thus a complete charge of fresh base is required for each reaction.
2. In Hirai et al.'s process it is preferred, from the viewpoint of reaction yield, to carry out the process while gradually adding water to the reaction system (sentence bridging columns 7 and 8). The controlled addition of a liquid (or solid) reagent to a reaction mixture under pressure is an operation best avoided in a large scale industrial process for various reasons, e.g. routine process operability, capital cost, etc.
3. In Hirai et al.'s process the palladium catalyst is apparently inactivated during the process and/or work up. The spent catalyst is recovered as the hydrochloride of the metal chloride by suspending it in hydrochloric acid and using chlorine gas to oxidise it (column 9, line 65 to column 10, line 3). Palladium metal is expensive and it is important, in an industrial context, to be able to recover and re-use it. The processes described by Hirai et al. for catalyst recovery are not suitable for efficient and economical industrial manufacture.

Applicants have solved the problems associated with the process of Hirai et al. by devising a process suitable for scale up to an industrial level which (a) avoids the bulk handling of solids, (b) uses liquid reagents that are readily available and have physical properties suitable for the operation of the chemical reaction, and which are recoverable and recyclable within the process, and (c) allows recycling of the catalyst directly into the process without external treatment.

Applicants' process utilises a reaction medium comprising a tertiary alcohol and water in a defined molar ratio and a tertiary amine, allowing not only the 3-ISC to be

isolated in a good yield but also allowing the solvent, the base and the catalyst to be recycled directly into the process. Thus, at the end of the carbonylation reaction, the mixture may conveniently be treated with sodium hydroxide solution to extract the 3-ISC into the aqueous phase as the sodium *o*-hydroxyphenyl acetic acid salt; and simultaneously regenerates the tertiary amine base from the hydrochloride. The base is retained in the organic layer along with the tertiary alcohol and catalyst together with residual water. This organic layer can be separated and re-used for a further carbonylation, as is demonstrated in Example 7. Any residual tertiary alcohol and base in the aqueous alkaline phase can be recovered for re-use by distillation. The product (3-ISC) is then separated from the alkaline aqueous phase by acidification and solvent extraction.

To achieve an industrially acceptable yield of 3-ISC and a process that is suitable for large-scale manufacture, the use of a recyclable liquid organic base is desirable. The combination of conditions that this requires is not taught by Hirai et al. The nearest thing to a liquid base used by Hirai et al. is sodium hydroxide. Solid sodium hydroxide is used in Examples 6 and 8 to 10 but dissolves in the water present to become liquid. However, the yields obtained are unacceptably low, averaging 35.3% (see the footnote on page 2). This in itself would steer one skilled in the art away from using a liquid base.

Even if a skilled person were minded to replace Hirai et al.'s much preferred calcium hydroxide base with a tertiary amine, this in itself would not lead to Applicants' claimed invention process. The simple replacement of calcium hydroxide with a tertiary amine leads to a process which gives an unacceptable reduction in yield. Applicants process requires that in order to achieve an acceptable yield using a tertiary amine base, the water content of the reaction medium is crucial such that there should be present at least one mole of water present for each mole of tertiary alcohol. This is clearly not taught by Hirai et al. and there is no motivation in Hirai et al. that would lead one skilled in the art to select the combination of a tertiary amine in a process where the ratio of water to alcohol is in the range of 1:1 to 20:1.


Claims 1-15 also stand rejected under 35 U.S.C. §103(a) as being unpatentable over Hirai et al, and further in view of Jones et al.

Applicants submit that use of the combination of Jones et al. and Hirai et al. references is not relevant, as the Jones et al. reference was not published until March 4, 1999, after Applicants' first priority date of September 18, 1998. In any case, Jones et al. uses a different solvent system of saturated or aromatic hydrocarbons, or halogenated derivatives of them, such as methylene chloride, toluene or chloro- or fluorobenzene. Xylene is preferred and is used in all the examples (see page 1, lines 25-30).

In view of the above amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103(a). Early and favorable allowance is respectfully requested.

Respectfully submitted,

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